American Society for Investigative Pathology
Investigating the Pathogenesis of Disease

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The American Society for Investigative Pathology (ASIP) listened with interest to the March 2015 Secretary's Advisory Committee on Human Research Protections (SACHRP) discussion on the current lack of harmony between the regulatory requirements of the Health Insurance Portability and Accountability Act (HIPAA) and the Clinical Laboratory Improvement Act (CLIA). ASIP is a nonprofit educational 501(c)(3) organization primarily representing the academic pathology research community. We are a society of biomedical scientists who investigate disease, linking the presentation of disease in the whole organism to its fundamental cellular and molecular mechanisms. Our members use a variety of structural, functional, and genetic techniques, seeking to ultimately apply research findings to the diagnosis and treatment of patients. Many ASIP members serve in leadership positions providing oversight to clinical laboratory services and also conducting biomedical research utilizing human biospecimens. As such, ASIP believes that it is in a unique position to provide insight to SACHRP and DHHS leadership on the key issues involved in this discussion. We request that we be given the opportunity to address the entire Committee at a future meeting so that we can express our opinion and voice our concerns.

We hold the following core principles related to the discussion of disharmony between CLIA and HIPAA regulations, each of which is discussed in detail below.

- Laboratories providing patient care should be CLIA-certified.
- Different laboratory standards for patient care and for research are appropriate.
- CLIA itself values the difference between reporting of patient test results and research.
- Regardless of whether research is conducted in a HIPAA covered institution or in a non-covered institution, Institutional Review Boards (IRBs) should carefully consider the issues involved, approving a consent that informs the subject of potential risks and benefits.

- Research proposals should proactively address contingencies for findings that may have implications for clinical care (incidental findings).
- CLIA-certified laboratories should be the entities responsible for providing information that may, at some point in the future, be used in patient treatment.
- Release of individual laboratory results should occur within the same ethical framework developed for releasing other clinical data/observations gathered during a research study.
- Even when research is conducted in a CLIA-certified laboratory, ASIP generally discourages the release of individual research results to research participants because such release would require a costly reporting framework detracting from the economical use of limited research funds and may leave laboratories subject to expensive lawsuits from patients who have not fully comprehended the essential difference between clinical testing and research tests.
- In an era of decreased funding for scientific research, administrative burden and cost implications should be considered when determining an appropriate course of action.

Laboratories providing patient care should be CLIA-certified. ASIP agrees that laboratories performing tests on "materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of human beings"[1] are appropriately regulated through CLIA. CLIA certification is a key element of safe and effective patient care, supporting the return of the right information on the right patient. CLIA certification should be obtained by laboratories providing information used in the care of patients.

Different laboratory standards for patient care and for research are appropriate. Patient care standards are designed to ensure that the right result is provided to the right patient. Laboratory tests performed in CLIA-certified laboratories must meet analytic (accuracy of a measurement) and test (does the test measure what it is supposed to) validity standards. In addition, CLIA-certified laboratories strive to meet clinical validity (does the test measure a value associated with a clinical condition) standards. Test results must be reported to the ordering physician(s) with sufficient information for proper interpretation, including false positive and false negative rates and levels of confidence as well as considerations of differential diagnosis. CLIA standards set an appropriately high bar for clinical care and support careful communication allowing for appropriate incorporation of laboratory findings into the care and treatment of patients. The maintenance of CLIA certification requires ongoing substantial investment of training, professional expertise, and administrative oversight.

The goal of research laboratory testing, on the other hand, is to expand upon our generalizable knowledge base. Research sample testing procedures are designed to accurately capture data from specimens in aggregate. In many circumstances, there is no need to correlate results directly with an individual. Furthermore, the research itself may be focused on developing an improved laboratory test and sharing findings would be inappropriate, without adequate validation. The ability to conduct research on biospecimens in the aggregate is a cost effective means of gaining knowledge.

Both the National Institutes of Health[2] and the National Science Foundation[3] have recently expressed concern about the lack of research reproducibility in preclinical research and there are

[1] See 42 U.S.C. § 263 a(a)

[2] Collins F, Tabak LA: NIH plans to enhance reproducibility. Nature 2014, 505:612-613

[3] Reproducibility_NSFPlanforOMB_Dec31_2014.pdf

reports in the literature estimating that more than half of preclinical research studies cannot be reproduced. With this in mind, ASIP urges extreme caution in any discussion of return of research results to individuals.

CLIA itself values the difference between reporting of patient test results and research. Research laboratories are specifically defined as those that "test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients…"[4] CLIA also indicates that research facilities may be exempt from certification when performing human specimen research testing that does not provide patient specific results. CLIA standards are applicable, however, in situations in which research tests report identifiable patient specific results that will be or might be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."[5]

Regardless of whether research is conducted in a HIPAA covered institution or in a non-covered institution, Institutional Review Boards (IRBs) should carefully consider the issues involved in approving a consent that informs the subject of potential risks and benefits. ASIP believes that this responsibility is independent of whether an institution is covered under HIPAA. Obligations to research subjects should not vary depending upon the nature of the institution conducting the research. Instead, the nature of the research (clinical care versus research) should be the focus.

Research proposals should proactively address contingencies for findings that may have implications for clinical care (incidental findings). The best practice is to address foreseeable contingencies so that research participants are made aware, through the informed consent process, of what may occur and what may be required for follow-up, even in rare situations such as an incidental finding that can potentially affect the healthcare of the individual. The research plan should include a contingency plan for those extreme situations in which re-testing in a CLIA-certified laboratory to corroborate a research result may be appropriate and how that process should be approved. ASIP urges a reconsideration of CLIA statutory language that would make it possible to obtain additional biospecimens in order to utilize a CLIA-certified laboratory to confirm potentially clinically relevant results.

CLIA-certified laboratories should be the entities responsible for providing information that may, at some point in the future, be used in patient treatment. Findings in a non-CLIA certified laboratory, whether or not part of a HIPAA covered entity, should not be released to individual participants and this should be clearly stated: (1) in the research proposal that is reviewed by the IRB; and (2) in the informed consent process. Where there is consideration of follow-up of a result from a non-CLIA certified laboratory, an external review should take place prior to the release. The external review should be done by the research institution with the support and cooperation of the researcher.

Release of individual laboratory results should occur within the same ethical framework developed for releasing other clinical data/observations gathered during a research study. The release of individual research results should be governed by a broader policy currently being developed by SACHRP on the return of individual research results to subjects. Concerns about research reproducibility, administrative burden and potential liability, all of which are discussed in

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[4] 42 CFR § 193.3(b)(2)

[5] Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations, CLIA Resource, v. 12/10/2014 as accessed on April 7, 2015 from https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf

this letter, are reasonable concerns that may factor into a researcher's ability and willingness to release research results.

Even when research is conducted in a CLIA-certified laboratory, ASIP generally discourages the release of individual research results to research participants because such release would require a costly reporting framework detracting from the economical use of limited research funds and may leave laboratories subject to expensive lawsuits from patients who have not fully comprehended the essential difference between clinical testing and research tests. The potential for legal liability requires a careful discussion and analysis of the costs associated with provision of necessary legal protections to researchers who voluntarily provide research results. Finally, ASIP strongly urges that the return of individual research results be performed through a physician qualified to interpret the research results, including clear identification of risks such as the potential for false positive and/or false negative findings.

In an era of decreased funding for scientific research, administrative burden and cost implications should be considered when determining an appropriate course of action. It is ASIP's opinion that there is little to be gained and much to be lost by mandating that research testing be performed only in CLIA-certified laboratories. This would stifle innovation, dramatically increase costs, and essentially prohibit research on innovative testing modalities.

ASIP's recommendations are best summarized in a chart presented in Attachment 1, where we note the fundamental distinction between tests to be used in patient care and tests performed solely for research purposes. Where tests are to be used in the care and treatment of a patient, the test should be performed in a CLIA-certified laboratory and returned to the patient under HIPAA and CLIA provisions. Tests performed in a CLIA-certified laboratory solely for research purposes may be returned to individuals only under policies that are part of the research proposal and that are clearly communicated to the participant through the informed consent process.

In conclusion, ASIP encourages ongoing dialogue between SACHRP, patient advocate groups and relevant professional associations to develop alternative solutions around this issue. We stand ready to be part of this discussion.

ASIP appreciates the opportunity to raise our concerns with SACHRP and hope that our comments may further refine the ongoing discussions. We request that e be given an opportunity to present our comments at a future meeting of the SACHRP. Should you have questions or concerns, please feel free to contact Mark E. Sobel, MD, PhD at (301) 634-7130 or mesobel@asip.org.

Sincerely,

Mark E. Sobel, MD, PhD
Executive Officer

Enclosures:
Attachment 1
Attachment 2

RETURN OF RESEARCH RESULTS

RECOMMENDATIONS TO ASSIST IN RESOLVING CONFLICTS BETWEEN CLIA AND HIPAA

Laboratory where test is performed	Test result will be used in patient care	Test performed solely for research purposes and will not be used in patient care
CLIA-certified	Return to patient under HIPAA/CLIA provisions	Results should not be returned to participants except as clearly outlined in the research proposal and communicated through the informed consent process. Costs and legal liabilities associated with return of individual results and necessary changes in experimental design must be balanced against potential benefits.
Not certified	N/A	Results should not be returned to research participants and this should be clearly stated in the consent. In rare situations of an incidental result with potential clinical significance, follow the IRB-approved procedure for external review and possible re-testing in a CLIA-certified laboratory.

RETURN OF RESEARCH RESULTS

ILLUSTRATIVE EXAMPLES

Example 1

Study description: A CLIA-certified laboratory is interested in evaluating whether a new test can better determine which patients will successfully respond to a particular chemotherapy regimen. A key aspect of the research protocol is to correlate the test result with an individual's clinical outcome on a particular standard chemotherapy regimen.

Approved consent language: The consent used to gather the specimen was broad and stated that research findings will not be made available to patients.

Situation arising during the course of research: During IRB consideration of the study, the question is raised as to whether the results of the test would be included in the patient's medical record.

Conclusion: As the new test has not been validated, it is inappropriate to use this test in the course of patient care. As such, the test results will not appear in the medical record of any individual patient and will not be used in the course of patient care.

Example 2

Study description: A non-CLIA certified laboratory that is part of a HIPAA covered institution is using next generation sequencing to map whole exomes to study Alzheimer's disease. The study requires sequencing both parents and their adult offspring. There is a risk that the study may identify nonpaternity.

Approved consent language: The specimens are gathered under a consent specific to the study that states that findings are not disclosed to participants. Risks, including identification of nonpaternity, are explained in the consent.

Situation arising during the course of research: A research participant requests the results of his whole exome analysis.

Conclusion: The whole exome analysis is not provided.

Example 3

Study description: As part of a sickle cell hematopathology study, a non-CLIA certified laboratory performs complete blood counts (CBC) on both identifiable individuals suffering from sickle cell disease and identifiable control subjects.

Approved consent language: The consent noted the risk of an incidental finding and described how it would be handled (external review, possible re-testing in a CLIA-certified laboratory, possible re-contact with subject to arrange for re-testing).

Situation arising during the course of research: The CBC reveals an incidental finding of significant anemia in a control subject. There is not sufficient sample remaining to have it verified by a CLIA-certified laboratory.

Conclusion: Researcher follows the process approved by the IRB and described in the consent: (1) external review of the finding to determine if it warrants corroboration; (2) if so, control subject is contacted by a healthcare provider, asking for permission to verify a potential research finding of as yet uncertain significance; and (3) if permission is granted, control subject is directed to a CLIA-certified laboratory that is part of the same institution for a CBC and follow-up with a healthcare provider. The result obtained by the non-CLIA certified laboratory is not part of the medical record and is not disclosed to the research subject. The report of the CBC obtained in the CLIA-certified laboratory is part of the medical record and can be disclosed under HIPAA.